Marked Inflammatory Sequelae to Implantation of Biodegradable and Nonbiodegradable Polymers in Porcine Coronary Arteries

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Background With the thrombogenic tendency and permanent implant nature of metallic stents, synthetic polymers have been proposed as candidate materials for stents and local drug delivery designs. We investigated the biocompatibility of several synthetic polymers after experimental placement in the coronary artery.

Methods and Results Five different biodegradable polymers (polyglycolic acid/polylactic acid [PGLA], polycaprolactone [PCL], polyhydroxybutyrate valerate [PHBV], polyorthoester [POE], and polyethyleneoxide/polybutylene terephthalate [PEO/PBTP]) and three nonbiodegradable polymers (polyurethane [PUR], silicone [SIL], and polyethylene terephthalate [PETP]) were tested as strips, deployed longitudinally across 90° of the circumferential surface of coil wire stents. Appropriately sized polymer-loaded stents were implanted in porcine coronary arteries of 2.5- to 3.0-mm diameter. Four weeks after implantation, stent patency was assessed by angiography followed by microscopic examination of the coronary arteries. The biodegradable PCL, PHBV, and POE and the nonbiodegradable PUR and SIL evoked extensive inflammatory responses and fibrocellular proliferation (thickness of tissue response: 0.79±0.22, 1.12±0.01, 2.36±0.60, 1.24±0.36, and 1.43±0.15 mm, respectively). Less but still severe responses were observed for the biodegradable PGLA and PEO/PBTP (0.46±0.18 and 0.61±0.23 mm, respectively) and for the nonbiodegradable PETP (0.46±0.11 mm).

Conclusions An array of both biodegradable and nonbiodegradable polymers has been demonstrated to induce a marked inflammatory reaction within the coronary artery with subsequent neointimal thickening, which was not expected on the basis of in vitro tests. The observed tissue response may be attributable to a combination of parent polymer compound, biodegradation products, and possibly implant geometry. (*Circulation.* 1996;94:1690-1697.)

Key Words • stents • arteries • angioplasty • coronary disease

Percutaneous transluminal coronary angioplasty to deform or ablate obstructive coronary atherosclerotic narrowing is performed increasingly with inflatable balloons, excisional and rotational atherectomy devices, stents, and lasers. Progress has been made since the introduction of this technology with respect to procedural success as well as the increasing complexity of coronary lesions treated. Early coronary reocclusion as well as late restenosis, however, remain limitations of PTCA. Recently, high-dose systemic antiplatelet drug therapy has been shown to limit early complications after PTCA by ≈35%; however, bleeding complications have ensued.[1] The beneficial effect was shown to be sustained, as a trend toward a reduction in the need for later revascularization was also observed.[2] The only approach proven to reduce the incidence of late restenosis (by 30%) is the use of coronary stents.[3,4] However, despite recently promoted high-pressure deployment and antiplatelet therapy with aspirin and ticlopidine, the use of stents is not free from complications, with an incidence rate of ≤20% at 6 months.[5-7] Therefore, a combination of drugs and stents has been touted as a possibility to overcome both early and late complications of PTCA.[8,9]

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Synthetic polymers have been proposed as a solution to improve the quality of stents, to serve as a vehicle for local (high-dose and site-specific) drug delivery, or both.[10,11] Therefore, efforts are under way to develop polymer compounds that can be implanted within the coronary artery.[12-17] In addition, biodegradable polymers may be formulated with dispersion of drug within the polymeric preparation. Drug release would then occur by diffusion through and/or breakdown of the base polymer. Several biodegradable polymers have been screened for medical-device applications, and a few have been used for local (subcutaneous) drug delivery systems or wound healing. It is unknown, however, whether tissue compatibility data generated from in vitro systems, animal subdermal implant models, or nonvascular human application adequately reflect blood compatibility.[18,19] Therefore, we studied the biocompatibility of five biodegradable polymers and three nonbiodegradable polymers after implantation within porcine coronary arteries.

Methods

Polymer Test Samples

Five different biodegradable polymers were studied (Table 1). They were selected by known medical application and favorable screening results in vitro and in vivo.[20-32] To control for the effects of the biodegradation process, three different

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Selected Abbreviations and Acronyms

LAD = left anterior descending coronary artery
LCx = left circumflex coronary artery
PCL = polycaprolactone
PEO/PBTP = polyethyleneoxide/polybutylene terephthalate
PETP = polyethylene terephthalate
PGLA = polyglycolic acid/polylactic acid
PHBV = polyhydroxybutyrate valerate
POE = polyorthoester
PTCA = percutaneous transluminal coronary angioplasty
PUR = polyurethane
RCA = right coronary artery
SIL = silicone

nonbiodegradable polymers were also tested in the same experimental protocol.[33-35]

The polymer specimens were processed to obtain strips 75 to 125 μm in thickness. The strips were cast longitudinally onto a balloon-expandable stent (Wiktor, Medtronic Inc) that served as the vehicle for polymer deployment. The polymer covered ≈90° of the stent circumference (Fig 1). Polymer-loaded stents were mounted on standard angioplasty balloon catheters (manufacturer-specified balloon diameter, 3.0 to 3.5 mm). The implant systems were produced in a clean laboratory environment but not sterilized because of concern about changing the physicochemical properties of the polymers.

Animal Preparation

Experiments were performed in farm-bred pigs (weight, 20 to 30 kg) fed a normal, nonatherogenic chow. The investigations were performed according to the *Guide for the Care and Use of Laboratory Animals* (NIH publication 85-23, 1985), and the protocol was approved by the Experimental Animals Ethics Committee of the three participating centers. The experimental protocol of this first multicenter animal trial of restenosis was uniform for the three study sites, and each site strictly adhered to this protocol. The polymers studied at each center were as follows: polyglycolic acid/polylactic acid (PGLA), polyorthoester (POE), and polyurethane (PUR) (Cleveland Clinic); polyhydroxybutyrate valerate (PHBV) and silicone (SIL) (Mayo Clinic); and polycaprolactone (PCL), polyethyleneoxide/polybutylene terephthalate (PEO/PBTP), and polyethylene terephthalate (PETP) (Thoraxcenter).

After an overnight fast, the animals were sedated. After endotracheal intubation, the pigs were connected to a ventilator, and anesthesia was maintained with gas anesthetics. After administration of antibiotic prophylaxis, arterial access was obtained under sterile conditions by femoral or carotid artery cutdown. Thereafter, angiography was performed to select the part of the coronary tree in which to leave the implant. Heparin (5000 IU) was administered during the procedure only. Aspirin (325 mg) was given before the procedure and continued daily during the 4-week follow-up period.

Polymer-Loaded Stent Implantation

The method of implantation of the polymer-loaded stent in porcine coronary arteries was similar to that described for the conventional stent.[36] Briefly, on the basis of the angiograms, at least one segment in one of the three epicardial coronary arteries (LAD, LCx, and RCA) was selected with a diameter of ≈2.5 to 3.0 mm. Thereafter, an angioplasty catheter with the polymer-loaded stent crimped on its deflated balloon was advanced to that site for implantation over a standard PTCA guidewire. The balloon was inflated to a maximal pressure of 8 atm for 30 seconds, deflated, and slowly withdrawn, leaving the stent in place. This procedure was eventually repeated in a second coronary artery. After repeat angiography of the stented coronary arteries to confirm patency, the arteriotomy was repaired, the skin was closed, and the animals were allowed to recover from anesthesia.

Follow-up Examination

The catheterization procedure for follow-up angiography at 4 weeks was identical to that described above. Coronary angiography was performed in the same projection as used during implantation. Thereafter, the thorax was opened by a midsternal split and a lethal dose of sodium pentobarbital was injected intravenously, immediately followed by in situ fixation of the coronary arteries according to routine procedures in the three study centers, with use of a pressure of ≈120 mm Hg. Subsequently, the stented vessels were dissected free and placed in 4% formaldehyde in phosphate buffer (pH 7.3) for ≥48 hours in preparation for microscopy.

TABLE 1. Biodegradable and Nonbiodegradable Polymer Test Samples

Chemical Name	Abbreviation	Structure	MW, kD	Degradation Rate	Medical Application	Reference
Biodegradable polymers						
Polyglycolic acid/polylactic acid copolymer (85/15)	PGLA	Amorphous	40-100	100% in 60-90 days (rat SC)	Sutures; fracture fixation; oral implants; drug delivery microspheres	20-24
Polycaprolactone	PCL	Semicrystalline	40-72	50% in 4 years (rat SC)	Contraceptive delivery implant; prosthetics; sutures	25,26
Polyhydroxy-butyrate/-valerate copolymer (78/22)	PHBV	Semicrystalline	100-760	0-20% in 26 weeks (rat SC)	Sutures; drug delivery microspheres	27,28
Polyorthoester	POE	Amorphous	100-130	60% in 46 weeks (saline bath 37°C)	Prosthetic nerve grafts; contraceptive delivery implant	29,30
Polyethyleneoxide/polybutylene terephthalate copolymer (30/70)	PEO/PBTP	Semicrystalline	Not available	50% in 52 weeks (rat middle ear)	Tympanic membrane	31,32
Nonbiodegradable polymers						
Polyurethane	PUR	Semicrystalline	48	NA	Artificial heart; vascular prostheses; pacemaker lead insulation	33
Poly(dimethyl)-siloxane	SIL	Amorphous	Not available	NA	Drug-eluting pacing lead; electrostimulation device	34
Polyethene terephthalate	PETP	Semicrystalline	26	NA	Vascular prostheses; heart valve sewing ring; annuloplasty ring	35

MW indicates molecular weight; NA, not applicable; and SC, subcutaneous.

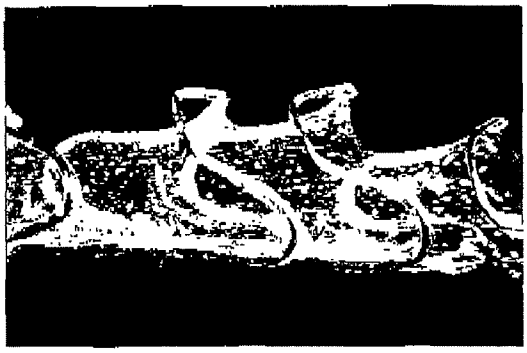


FIG 1. Polymer test strip cast asymmetrically on the coil stent vehicle. Magnification ×20.

Microscopic Examination

Serial sections over the entire length of the polymer-containing coronary segment were embedded in methacrylate or, after removal of the metal stent wires, paraffin. After routine staining (hematoxylin-azaphloxin or hematoxylin-eosin) and application of an elastin stain (resorcin-fuchsin or elastica-van Gieson), at least three representative sections of each artery were examined at each center for fibrocellular tissue response and inflammatory changes on the polymer side, after which the slides were sent to one institute (Erasmus University Rotterdam) for central review.

Morphometry

For the measurement of the constituent layers of the arterial wall, at least three elastin-stained sections from the proximal, central, and distal parts of each stented coronary segment were examined. The extent of the tissue response at the side of the polymer test sample was assessed as shown in Fig 2. In each section, only the middle area at the polymer side was analyzed so that the potential damaging effect of the polymer edges could be excluded.

Gram Staining

To check for bacterial contamination of the implants, alternate histological sections of the stent-containing segments with the polymers PGLA, POE, and PUR were also stained with Gram's stain.

Statistical Analysis

All data are expressed as mean±SEM. Histological measurements were analyzed by unpaired Student's t test. Because of repeated testing, only values of $P<.01$ were considered statistically significant (Bonferroni correction).

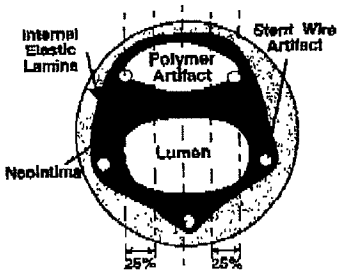


FIG 2. Diagrammatic representation of a coronary artery cross section with the polymer test sample removed. The arrows at both the polymer and opposite sides indicate the central 50% of the tissue reaction that was used for the assessment of neointimal area and thickness.

FIG 3. Macroscopy of transverse section through a PHBV test sample–containing coronary artery 4 weeks after implantation. The asymmetric luminal narrowing is consistently associated with the polymer strip (between arrowheads). Magnification ×40.

Results

Polymer Test Sample Implantation

For each polymer, 5 to 10 test samples were placed in four to six animals (Table 2). In all but five cases, the polymer test sample could be placed in the predetermined coronary segment. Damage to the metal stent or premature detachment of the polymer strip was the cause of failure in three cases. In two cases, air embolism during angiography caused the implantation procedure to be aborted. Angiography after successful implantation showed that all coronary arteries were patent, with no signs of intraluminal defects.

Follow-up and Restudy at 4 Weeks

Stent occlusion resulting in premature death of the animal occurred in three groups (PHBV, PEO/PBTP, and SIL) in the first 48 hours after implantation (Table 3). In the groups receiving PGLA, PCL, POE, PUR, and PEO/PBTP, silent occlusion of one of the stents was angiographically demonstrated at 4 weeks. When both early and late stent occlusion were considered together, the arterial patency rate at 4 weeks varied between 70% (PEO/PBTP) and 100% (PGLA, POE, PUR, and PETP), with other groups having one or two arteries occluded (Table 3). In most other cases, repeat angiography showed an eccentric lumen reduction at the site of the test sample implant at 4 weeks.

Histology

Macroscopic examination demonstrated that the eccentric lumen reduction apparent on angiography was due to a localized tissue reaction on the polymer side of the implants (Fig 3). Light microscopy confirmed that the eccentric tissue response was located mainly on the polymer side. All polymers seemed to evoke a similar reaction; only the extent of the reaction differed (Fig 4), ranging from a relatively benign response (Fig 4A) to a malignant or severe inflammatory response (Fig 4D). Thrombus remnants containing mainly fibrin but also platelet and erythrocyte remnants and hemosiderin deposits were present near the polymer strips. At the interface between polymer and tissue, multinucleated giant

TABLE 2. Implantation Data of Polymer-Loaded Stents

Polymer	Animals, n	LAD Stents	LCx Stents	RCA Stents	Failures to Implant
PGLA	4	4	0	4	None
PCL	6	2	4	2	One stent damaged
PHBV	4	3	0	2	None
POE	4	4	0	4	One air embolism; one polymer strip detachment
PEO/PBTP	5	5	2	3	None
PUR	4	4	1	3	One air embolism; one polymer strip detachment
SIL	4	1	2	2	None
PETP	6	3	1	3	None

cells and macrophages surrounded this proteinaceous debris (Fig 5). However, signs of acute inflammation were also observed frequently, evidenced by granulocytes (predominantly eosinophils), lymphocytes, and occasional plasma cells. This thrombotic and inflammatory reaction was seen on all sides of the polymer strips, ie, also toward the adventitial side.

A thick layer with a predominantly fibrocellular component was seen around this layer but was most pronounced between the polymer and the lumen. This layer contained smooth muscle cells (confirmed by immunostaining with smooth muscle cell–specific α-actin antibody) in a matrix of collagen and proteoglycans with many neocapillaries and spilled over to the bare wire sites of the specimen. Moderate to severe disruption of the architecture of the arterial wall was present in most specimens. This consisted of rupture or lysis of the elastic membranes and in some cases also of the media and was always accompanied by adventitial inflammatory infiltrates (Fig 5). This pattern of thrombus remnants, acute and chronic inflammation, and fibrocellular hyperplasia was observed with both biodegradable and nonbiodegradable polymers.

Morphometry

Thickness and area of the tissue response per polymer test sample are summarized in Table 4. Regardless of the type of polymer, the vessel wall reaction was more pronounced on the polymer than on the metal wire alone. The thickness or area of the tissue reaction to PHBV, POE, PUR, and SIL was significantly larger than the reaction to all other polymers. No significant differences between the other polymer groups were observed.

Gram Staining

Signs of bacterial contamination were not observed in any of the samples that underwent Gram staining.

Discussion

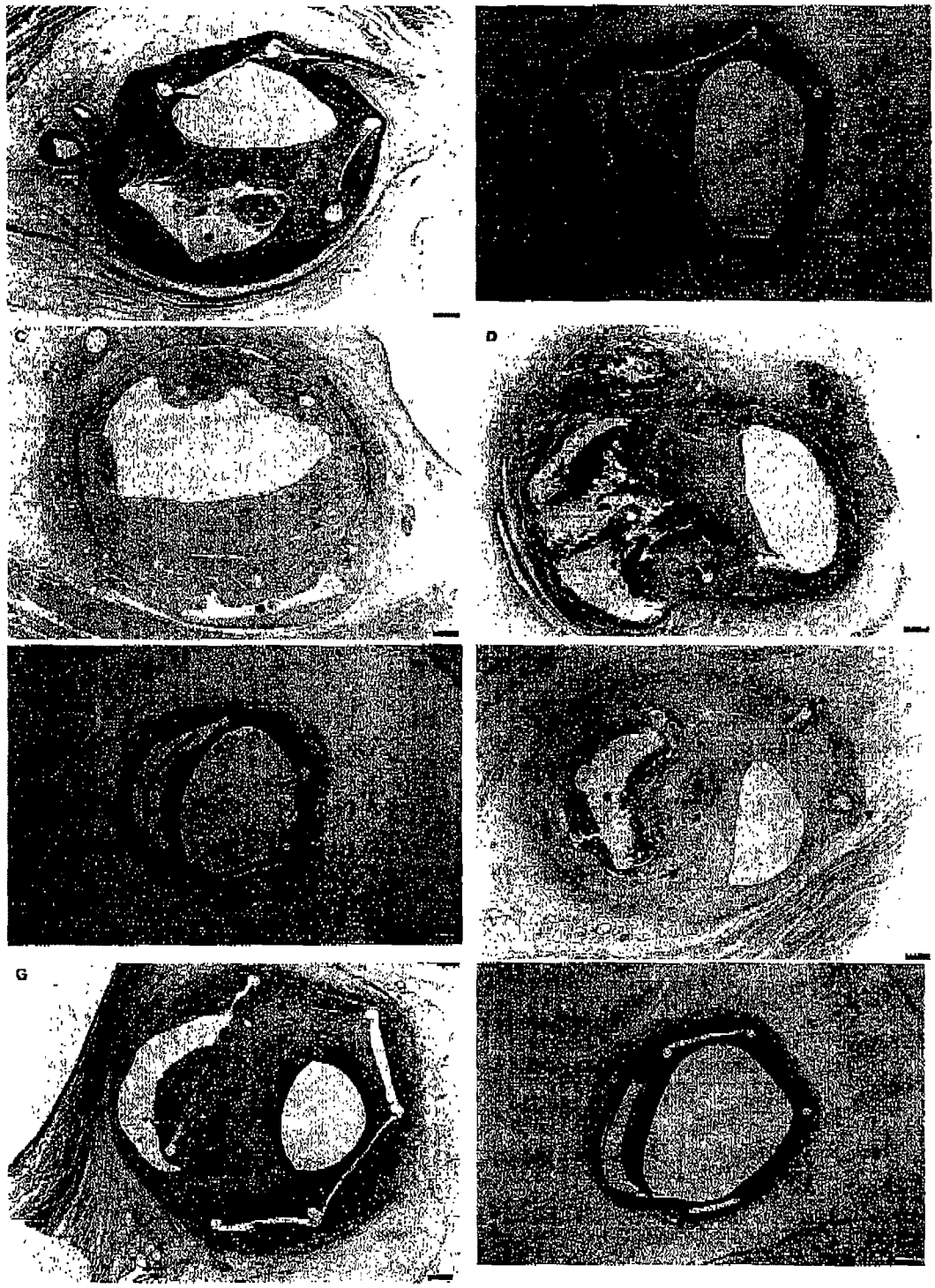
Study Objective and Design

The purpose of this study was to screen which polymers may be candidate materials for construction of new stents or local drug delivery modalities. Therefore, polymers were screened for their biocompatibility in the coronary circulation in a format that bypassed the need to construct new stents. In addition, because a metal stent was used as the carrier, the reactions to polymer and metal could be compared. The polymers were selected because of favorable results of in vitro test systems or (preliminary) medical applications.[20-35] This choice was also based on the premise that the biodegradation rate of the polymers should be in the range of months, to allow early disappearance of the implant or a rapid rate of drug diffusion from the polymeric matrix. The reasoning was that the mechanical scaffolding function of stents would only be needed in the first few weeks after angioplasty, and the local tissue response to an implant or after arterial injury (PTCA) could be influenced by drugs in the early phase.[17]

A unique feature of the present approach is that we chose to perform this study using identical experimental protocols at three centers experienced in the evaluation of new vascular techniques. Therefore, we were able to screen a variety of polymers within a limited period of time while at the same time allowing comparison of results between the polymers and the centers involved.

TABLE 3. Angiographic Patency and Complications During Follow-up

Polymer	Angiographic Patency at 4 Weeks	Complications	Time to Occlusion (Cause of Occlusion)
PGLA	8/8	None	Not applicable
PCL	8/8	One stent, angiographic severe narrowing at 4 weeks	(Proliferative response)
PHBV	5/7	One animal died of acute occlusion of two stents	<24 hours (platelet thrombus)
POE	8/8	One stent subtotally narrowed at 4 weeks	(Proliferative response)
PEO/PBTP	7/10	One animal (two stents) died of thrombosis of both implants	<8 hours
		One animal (two stents) died at 3 weeks (only one stent occluded)	(Severe inflammatory response)
PUR	8/8	None	Not applicable
SIL	4/5	One animal died with acute occlusion (one of two stents)	<24 hours (platelet thrombus)
PETP	7/7	None	Not applicable



Main Findings

The main study results of this multilaboratory approach are summarized as follows: (1) after a follow-up period of only 4 weeks, all polymer implants were associated with a significant inflammatory and proliferative response; (2) this response was observed with both biodegradable and nonbiodegradable polymer implants; (3) in some groups, implants were complicated by acute thrombotic vessel occlusion, although with no more frequency than that expe-

FIG 4. (Facing page.) Various tissue responses to the individual biodegradable (A through E) and nonbiodegradable (F through H) polymer test samples. In each panel, the bar indicates 375 μm. A, PGLA. The large open area was occupied by the polymer (*) and proteinaceous debris (arrow) and covered by a distinct fibrocellular layer. (Elastic stain.) B, PCL showed a smaller polymer artifact (*) but a more pronounced eccentric fibrocellular response. (Hematoxylin-eosin-stain.) C, PHBV. At the site of the polymer implant (*), the media ruptured (arrowhead), but at the opposite side, lysis of the elastic membranes had occurred (arrow) as a phenomenon secondary to the inflammatory response. (Elastic stain.) D, POE induced an immense inflammatory response with a granulomatous appearance (arrowhead) that extended into the adventitia and resulted in destruction of the architecture of the vessel. (Elastic stain.) E, PEO/PBTP. The vascular response to this polymer (arrow) was limited in nature and had a more benign character. (Elastic stain.) F, PUR demonstrated a circumferential inflammatory reaction to both the polymer (*) and damaging bare wire (arrowheads) that extended into the neointima (arrow). (Hematoxylin-eosin-stain.) G, SIL. In contrast to the reaction to PUR, the intense inflammatory response was restricted to the polymer but with a circumferential fibrocellular response. (Elastic stain.) H, PETP showed a benign tissue response and a limited neointimal growth. (Hematoxylin-eosin stain.)

rienced with stainless steel coronary stents.[17,38] Occlusion occurred more frequently, however, than with the tantalum carrier stent alone.[36]

Polymer Implants in the Coronary Circulation

Implants in the cardiovascular system are more demanding than those in other parts of the human body. The requirement for blood compatibility is added to the requirements for biological performance, absence of toxic reactions (toxic, immunologic, carcinogenic), and long-term mechanical properties (fatigue life, wear resistance, kink resistance) in this dynamic environment.[39] This means favorable behavior is required in an environment in which complex and integrated cellular and humoral systems (coagulation, complement, and immune systems) unite to isolate and exclude the foreign body from incorporation into the vascular wall.[35] Therefore, in retrospect, it is not surprising that polymer implants in the coronary circulation elicit a more severe reaction than that predicted from subcutaneous implants. In three groups (PHBV, PEO/PBTP, and SIL), early thrombotic occlusion was observed (5 [23%] of 22 stents). This is not an exceptionally

TABLE 4. Thickness and Area of Neointima Covering Polymer Sample and Bare Wire

Polymer	Neointimal Thickness: Polymer, mm	Neointimal Area: Polymer, mm²	Neointimal Thickness: Bare Wire, mm	Neointimal Area: Bare Wire, mm²
PGLA	0.46±0.18	0.34±0.15	0.08±0.03	0.09±0.05
PCL	0.79±0.22	0.70±0.23	0.11±0.06	0.04±0.03
PHBV	1.12±0.01	3.32±0.71*	0.21±0.14	0.36±0.02*
POE	2.36±0.60*	1.56±0.55*	0.38±0.17*	0.23±0.11
PEO/PBTP	0.61±0.23	0.52±0.29	0.14±0.09	0.09±0.05
PUR	1.24±0.36*	0.89±0.36	0.34±0.26	0.22±0.17
SIL	1.43±0.15*	3.13±1.1*	0.41±0.17*	0.66±0.19*
PETP	0.46±0.11	0.35±0.11	0.11±0.06	0.06±0.04

*P<.01 vs PGLA, PCL, PEO/PBTP, and PETP.

high number, because earlier studies in the same model reported even higher rates of thrombosis with stainless steel stents.[17,38] Moreover, during the initial clinical experience with the Palmaz-Schatz stent, an 18% incidence of subacute closure was observed when anticoagulation treatment was withheld.[40] Furthermore, it has been reported recently[41] that noncoated, slotted-tube stents show a 42% thrombotic occlusion rate in the rabbit iliac model.

However, local mechanical and hemodynamic factors may influence the success or failure of a specific material.[42,43] For instance, vascular grafts of PETP (Dacron) seem to perform best in larger vessels, whereas in smaller vessels, expanded polytetrafluoroethylene (Gore-Tex) yields good results. However, in vessels <4 mm in diameter, all synthetic materials fail, and the use of vein grafts offers the best solution. Our results in the coronary circulation extend this effect of recipient vessel diameter to the coronary circulation.

The results of the present study may only be applicable to the specific polymers investigated. Differences in molecular weight, polymerization catalysts, plasticizers, and fillers may all change the physicochemical behavior of the implants. Studies by others who used a PGLA stent yielded superior results,[12] but the toxicity of PGLA microspheres in smooth muscle cell culture has also been reported recently.[44] Furthermore, the use of PETP stents of different sources resulted in equivocal vascular responses.[15,16]

In the present study, a significant inflammatory response was observed with all implanted polymers. In all cases,

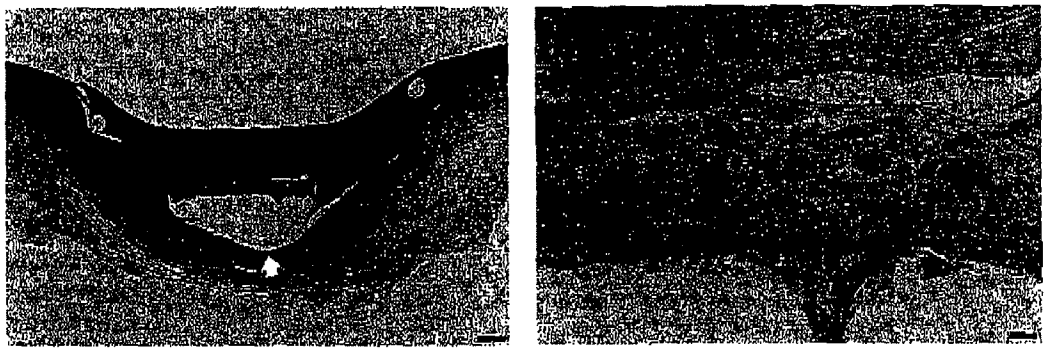


FIG 5. A, A segment of the PETP test sample shows laceration of the internal elastic membrane and media and obliteration of the external elastic membrane (arrow). (Elastic stain; bar=200 μm.) B, Detail of the cadre indicated in Fig 5A showing fibrin thrombus remnants (F), neovascularization (N) with ongoing leukocyte infiltration (arrowhead), and abundant multinucleated macrophage giant cells (G). (Hematoxylin-eosin stain; bar=20 μm.)

this consisted of a chronic inflammatory reaction with an acute component and a persistent foreign-body response. In most cases, a substantial part of the overall inflammatory and proliferative response may have been aggravated by damage due to the asymmetric geometry of the implant. It is very likely that the aggressive inflammatory response may have increased the injury to the arterial architecture by the action of released proteases and elastases. This may have been influenced by by-products of the polymer. A role for greater stretch injury of the polymer side of the stent cannot be excluded, but it seems more likely that the presence of the hard polymer structure merely prevented overstretch on that side. Indeed, after in vitro expansion of some stent specimens by inflation, followed by removal of the balloon, it was evident by subsequent high-power microscopy that the polymer strip covered a smaller part of the circumference than in the unexpanded condition. In addition, the uncovered part expanded more than the part covered by the polymer. The possibility that this acute damage adds to the final outcome should be substantiated by acute experiments in future studies testing the intracoronary biocompatibility of other synthetic polymers.

In addition to the general reaction to the bulk material and the physicochemical properties of the implant surface, the surface texture could be an important determinant of the early reaction.[37] A limitation of the present study is that we cannot retrospectively correlate the overall response with its several components.

It should also be emphasized that the implants in the present study were not sterilized but were manufactured in a clean laboratory environment. This may have influenced the response. Gram staining in those polymer samples that demonstrated the most vigorous responses, however, did not show bacterial contamination. Furthermore, it has been shown that the addition of steroids to one of the polymers ameliorated the inflammatory response.[43] However, this does not exclude completely the possibility of bacterial or nonbacterial contamination.

Conclusions

The present study demonstrates the marked inflammatory and neointimal response to an array of biodegradable as well as nonbiodegradable polymers after implantation in the porcine coronary artery. This reaction must be fully understood biologically before we can make use of these or other polymers as implant materials in stents or drug delivery devices.

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JACC cardiovascular Interventions

The GENESIS (Randomized, Multicenter Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent System in Patients with De Novo Lesions of the Native Coronary Arteries) Trial

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The GENESIS (Randomized, Multicenter Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent System in Patients with De Novo Lesions of the Native Coronary Arteries) Trial

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Antwerp, Genk, and Leuven, Belgium; Southampton, United Kingdom; Berlin and Hamburg, Germany; Toulouse, France; Jerusalem, Israel; Warren, New Jersey; Stanford, California; and New York, New York

Objectives The aim of this study was to compare, in a randomized multicenter trial, paclitaxel-eluting stents (CoStar, Conor Medsystems, Menlo Park, California) versus pimecrolimus-eluting stents (Corio, Conor Medsystems) versus stents with dual elution of both drugs (SymBio, Conor Medsystems) in native coronary arteries.

Background The CoStar cobalt-chromium reservoir-based stent platform, eluting paclitaxel in a controlled way via a bioresorbable polymer, reduces restenosis versus its respective bare-metal stent. The reservoir system allows the use of other drugs targeted to different mechanisms involved in the process of vascular restenosis and simultaneous loading of multiple, synergistic drugs.

Methods Patients with single de novo lesions were asymmetrically randomized to 1 of the 3 types of stent (1:2:2). Six-month coronary angiography was planned in all. The primary analysis was a noninferiority test for the primary end point of 6-month angiographic in-stent late lumen loss of Corio versus CoStar and SymBio versus CoStar. Secondary end points included binary angiographic restenosis and major adverse clinical events (cardiac death, myocardial infarction, target vessel revascularization).

Results The trial was prematurely suspended after 246 patients were enrolled (planned enrollment 375 patients): 49 patients received CoStar, 97 received SymBio, and 100 received Corio. In-stent late loss was significantly reduced with CoStar versus either SymBio or Corio (0.58 ± 0.58 mm vs. 0.96 ± 0.73 mm and 0.58 ± 0.58 mm vs. 1.40 ± 0.67 mm, $p < 0.001$ for both comparisons). Binary in-stent restenosis rates were, 7.1%, 20%, and 40.9%, respectively ($p < 0.001$ for both comparisons); 6-month major adverse cardiac event rates were, 2.0%, 14.4%, and 39.0%, respectively ($p < 0.001$ for both comparisons).

Conclusions Stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic noninferiority when compared with paclitaxel-eluting stents. (A Randomized, Multi-Center Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent Systems; NCT00322569) (J Am Coll Cardiol Intv 2009;2:205–14) © 2009 by the American College of Cardiology Foundation

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The CoStar stent (Conor Medsystems, Menlo Park, California) is a cobalt chromium alloy stent platform designed to elute paclitaxel without the use of a surface polymer and drug coating but with a technology consisting of multiple laser-cut reservoirs within the stent struts (Fig. 1). These reservoirs are filled with a polymer/drug matrix consisting of a bioresorbable poly-lactic-co-glycolic polymer and paclitaxel. The drug elution occurs with both directional and kinetic control. The CoStar paclitaxel-eluting stent (PES) has been proven superior to the respective bare cobalt chromium stent in reducing angiographic restenosis and repeated revascularizations at 8 months (1).

Whereas the CoStar PES failed to demonstrate noninferiority to the first-generation Taxus PES (Boston Scientific, Maple Grove, Minnesota) for the primary end point of 8-month major adverse cardiac events (MACE) in the COSTAR (Cobalt Chromium Stent with Antiproliferative for Restenosis) II trial (2), the concept of reservoir technology of the stent, associated with the bioresorbable polymer delivery matrix, still offers the potential for alternative dose kinetic and elution profile improvements aimed at developing more effective and safer drug-eluting stents. Indeed, this technology allows loading and independent elution control of drugs targeting various mechanisms involved in the restenotic process. It also permits simultaneous independent delivery from a single stent of more than 1 therapeutic agent by placing different polymer/drug combinations in alternate, adjacent reservoirs. This combined delivery can concurrently address multiple physiologic stimuli responsible for the pathological events after stent implantation (3). Once the discharge of the loaded drug(s) is complete, the polymeric delivery matrix is absorbed, leaving a bare metal stent implanted.

Abbreviations and Acronyms

IVUS = intravascular ultrasound
MACE = major adverse cardiac event
MI = myocardial infarction
MLD = minimal luminal diameter
QCA = quantitative coronary angiography
PES = paclitaxel-eluting stent(s)
RVD = reference vessel diameter
TLR = target lesion revascularization
TVR = target vessel revascularization

Pimecrolimus is a compound, currently approved by the U.S. Food and Drug Administration and the European Medicines Agency for the topical treatment of atopic dermatitis. It is an anti-inflammatory agent with immunosuppressant properties, belonging to the class of calcineurin-inhibitors. Pimecrolimus inhibits the activation and proliferation of T-lymphocytes and the release of several growth factors. In addition, it targets mast cell release of pro-inflammatory mediators including histamine, cytokines, tryptase, and eicosanoids (4). Even though this agent does not exert any specific antiproliferative action, it might reduce the response of smooth muscle cell proliferation and neointimal hyperplasia by decreasing the localized inflammatory response and the resultant cascade of physiologic reactions secondary to the arterial injury caused by stent implantation (5,6).

This study was designed to determine the effectiveness of the anti-inflammatory molecule pimecrolimus alone and the synergistic combination of pimecrolimus with an antiproliferative agent such as paclitaxel (with the potential of simultaneous inhibition of 2 different mechanisms of restenosis), loaded in a drug-eluting stent with the Conor reservoir technology, on the neointimal reaction process assessed in humans by angiography.

Methods

The GENESIS (randomized, multicenter study of the pimecrolimus-eluting and paclitaxel-elutinG coronary stent system in patiENts with de novo lEsionS of the native coronary arterIeS) trial is a prospective, asymmetrically randomized, multicenter, open-label, 3-arm trial. The local ethics committee of every hospital enrolling patients approved the trial design.

Patient population. Patients were included if they were ≥18 years of age, with documented stable or unstable angina pectoris and had 1 de novo target lesion ≤25 mm in length, with a reference vessel diameter (RVD) of 2.5 to 3.5 mm and with visually estimated stenosis of ≥50% and <100%, localized in a native coronary artery.

Clinical exclusion criteria were: woman of childbearing potential; myocardial infarction (MI) within the previous 72 h; cardiogenic shock; documented left ventricular ejection fraction <25%; acute or chronic renal dysfunction (creatinine >2.0 mg/dl); cerebrovascular accident within the past 6 months; gastrointestinal bleeding within the past 3 months; thrombocytopenia (platelet count <100,000/mm³); contraindications to aspirin, clopidogrel, or contrast

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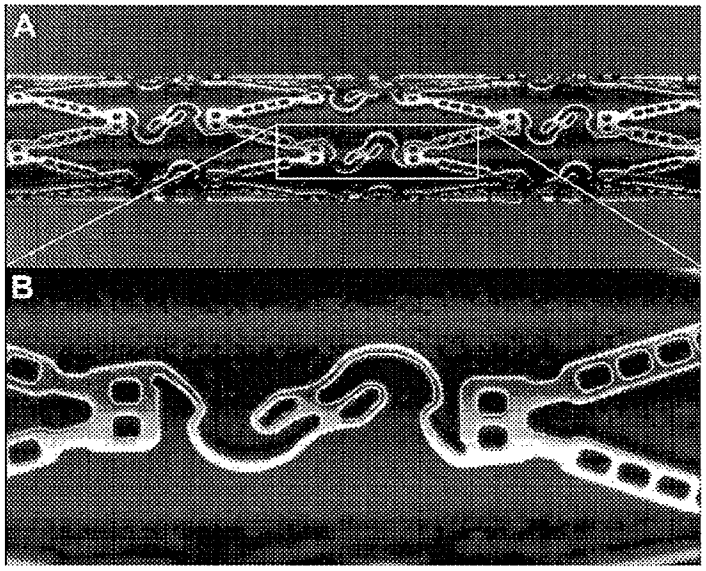

Figure 1. The CoStar Stent

Photograph of the CoStar stent (A). Magnification demonstrates the laser-cut reservoirs and a bridge element (B).

agents; known sensitivity to pimecrolimus, paclitaxel, cobalt chromium, or the poly-lactic-co-glycolic polymer; current assumption of colchicine; chronic systemic steroid or immunosuppressant therapy or systemic paclitaxel assumption within 12 months of the index procedure; life expectancy <24 months; or current participation in another investigational drug or device study. Angiographic exclusion criteria were: prior revascularization of the target vessel within the preceding 6 months, left main stenosis, ostial stenosis, bifurcation lesion, severe calcification or the presence of thrombus by visual estimation, pretreatment of the target lesion with any unapproved device or atherectomy or laser or cutting balloon, or prior brachytherapy in the target vessel. All enrolled patients provided written informed consent before the index procedure.

Procedural protocol, randomization, and follow-up. After percutaneous access was obtained, heparin was administered to maintain an activated clotting time >250 s (or >200 s if glycoprotein IIb/IIIa inhibitors were given). Glycoprotein IIb/IIIa inhibitors were given at the operator's discretion. Randomization was performed after baseline angiography was obtained, with a computerized central randomization service. Randomization was stratified by site and was accomplished at each site with an interactive voice randomization system. Eligible patients were randomized in a ratio of 1:2:2, respectively, to 1 of 3 treatment arms: CoStar PES (11-μg nominal dose in a 3.0 × 16 mm stent) or SymBio (Conor Medsystems) pimecrolimus/paclitaxel-eluting stent (162.5-μg pimecrolimus/11-μg paclitaxel nominal dose in a 3.0 × 16 mm stent) or Corio (Conor Medsystems) pimecrolimus-eluting stent (325-μg nominal dose in a 3.0 × 16 mm stent). Direct stenting was allowed and left at operator's discretion. In case of dissection or incomplete lesion coverage, the use of additional stents of the same type as the assigned stent was mandated. The first 30 patients enrolled into each arm were automatically allocated into an intravascular ultrasound (IVUS) substudy; IVUS was performed at the end of the procedure according to standard protocols after injection of 0.2 mg of nitroglycerin with a 20- to 40-MHz ultrasound probe and with a motorized pullback (speed: 0.5 mm/s). Aspirin (100 to 300 mg/day) was given daily, and clopidogrel (loading dose of at least 300 mg before procedure and 75 mg/day thereafter) was administered for at least 6 months in all patients. Serial blood samples for creatine kinase and creatine kinase-myocardial band were routinely obtained 8 to 12 and 16 to 24 h after the intervention.

Patients were evaluated clinically 1 and 6 months after the procedure. Coronary angiography was planned at 6 months (±30 days) in all patients, and IVUS analysis was planned in the cohort of patients receiving IVUS at baseline. Angiography was performed earlier if there were recurrent symptoms, but if restenosis was not found during this

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repeat angiography, a new angiography was done at 6 months.

Quantitative coronary angiography and IVUS analysis. Digital coronary angiograms were analyzed offline by an independent core laboratory, with a validated automated edge detection system (Medis, Leiden, the Netherlands) (7). Matched views were selected for angiograms recorded before and immediately after the intervention and at 6-month follow-up. Angiographic measurements were made both in the stent and in the stented segment (defined as the stent plus the 5-mm edges proximal and distal to the stent) during diastole with the contrast-filled guiding catheter for magnification calibration. In case overlapping stents were placed, a single in-stent value was measured, and the segment was considered as the entirely stented segment plus the 5 mm proximal to the more proximal stent and the 5 mm distal to the more distal stent implanted. Lesion RVD, minimal luminal diameter (MLD), percent diameter stenosis, and length were obtained at baseline. The RVD, MLD, and diameter stenosis were evaluated at the end of the procedure and at follow-up, for the in-stent, proximal edge, distal edge, and in-segment sections. Acute gain was defined as the difference between the in-stent MLD at the end of the intervention and the MLD at baseline. Late lumen loss was calculated as the difference in MLD between measurements immediately after the procedure and at follow-up. Binary angiographic restenosis was defined as diameter stenosis ≥50% by quantitative coronary angiography (QCA), at the follow-up angiogram (8). Restenosis patterns were assessed with the Mehran classification system (9).

Quantitative IVUS analysis was performed offline by an independent core laboratory, with validated software (echoPlaque, Indec Systems, Mountain View, California), allowing semi-automated detection of luminal and stent boundaries in reconstructed longitudinal planes. Volumetric quantitative coronary ultrasound analysis was obtained for vessel, stent, and lumen. Neointimal volume was computed as the difference between stent volume and lumen volume. Percent volume obstruction was calculated as the ratio between the neointimal volume and stent volume × 100. Incomplete stent apposition was defined as 1 or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut in a vessel segment not associated with any side branches (10).

End points and definitions. The primary end point of the study was 6-month in-stent late lumen loss (11,12). Secondary angiographic end points included in-segment late loss, in-stent and -segment binary restenosis (≥50% diameter stenosis), and in-stent and -segment MLD at 6 months after the procedure. Secondary IVUS end points were percent volume obstruction of the stent and incidence of late acquired incomplete stent-to-vessel apposition at 6 months. Secondary clinical end points were 30-day and 6-month MACE rates, defined as an adjudicated composite of cardiac death, new MI not clearly attributable to a nonintervention vessel, or clinically driven target vessel revascularization (TVR). In addition, clinically driven target lesion revascularization (TLR) at 6 months after the procedure was evaluated. Death was divided into 2 categories: cardiac and noncardiac. Cardiac death was defined as death due to acute MI or to a complication of the index procedure (including bleeding, vascular repair, transfusion reaction, or bypass surgery) or any death in which a cardiac cause cannot be excluded. Noncardiac death was defined as a death not due to cardiac causes. Myocardial infarction was defined in 2 ways: 1) Q-wave MI was diagnosed when chest pain or symptoms consistent with myocardial ischemia and new pathological Q waves in 2 or more contiguous electrocardiogram leads were present; and 2) non–Q-wave MI was defined as creatine kinase elevated >2 times the upper laboratory normal with the presence of elevated creatine kinase-myocardial band in the absence of new pathological Q waves. Clinically driven TVR and TLR were defined as revascularizations at the target vessel or lesion, respectively, associated with positive functional ischemia study or ischemic symptoms and an angiographic diameter stenosis ≥50% by QCA or revascularization of a target vessel or lesion with diameter stenosis ≥70% by QCA without either angina or a positive functional study. Stent thrombosis was defined according to the Academic Research Consortium criteria (13).

Additional secondary end points were device, lesion, and procedural success. Primary device success was defined as attainment of ≤50% in-stent residual stenosis of the target lesion with only the assigned device in the absence of device malfunction and device-related complication. Lesion success was defined as attainment of ≤50% residual stenosis of the target lesion with the assigned device or any percutaneous method. Procedure success was defined as attainment of a final lesion success and no in-hospital MACE.

An independent clinical events committee unaware of the patients' treatment assignment adjudicated all the clinical events, and an independent data safety monitoring board also reviewed clinical data periodically throughout the trial.

Statistical analysis. The study compared 2 experimental stents, SymBio and Corio, with the CoStar control stent. The comparisons of interest for the primary outcome of in-stent late loss were SymBio versus CoStar and Corio versus CoStar. The sample size of 375 patients (150:150:75) was based on the noninferiority hypothesis that the difference between late loss of SymBio or Corio and late loss of CoStar was ≤0.32 mm with a power of approximately 95%, assuming a pooled SD of 0.40 and a significance level of 0.025 for each comparison. All analyses were conducted according to the intention-to-treat principle. For the 2

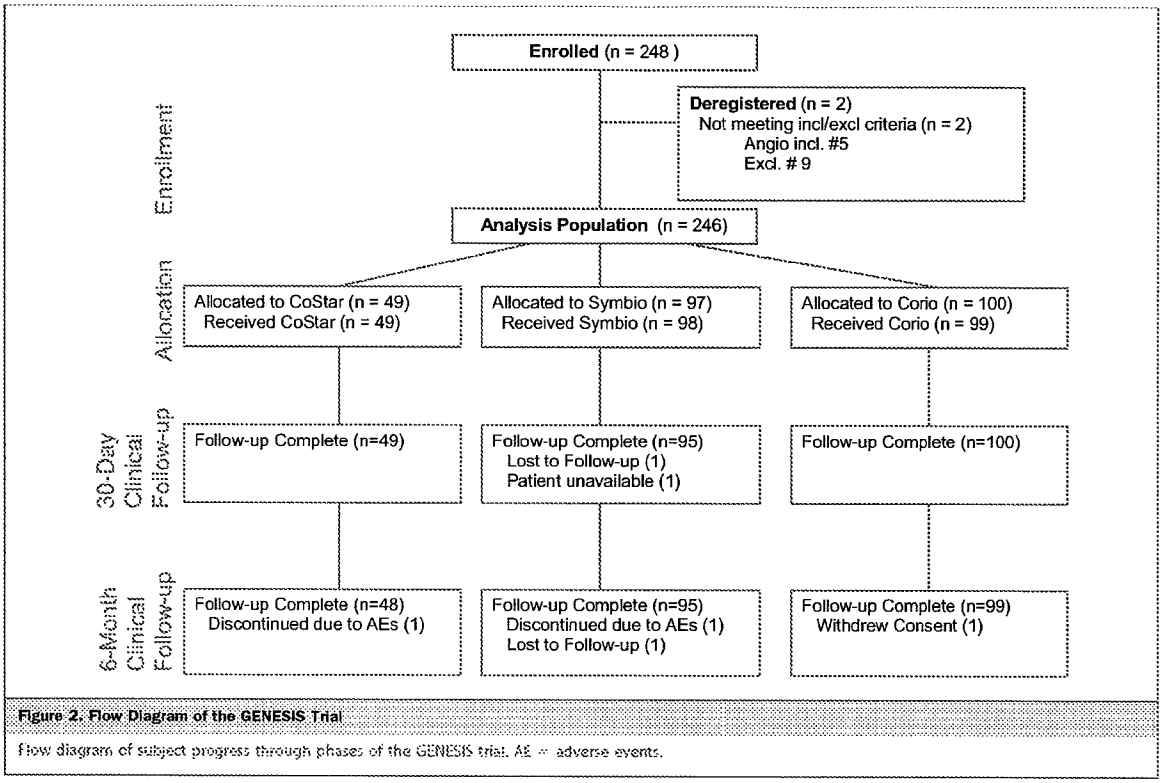

Figure 2. Flow Diagram of the GENESIS Trial

Flow diagram of subject progress through phases of the GENESIS trial. AE = adverse events.

primary comparisons, a 1-sided p value of ≤ 0.025 was considered significant. Analysis of variance tests and chi-square tests were employed, respectively, for continuous and categorical variables, to compare differences between the 3 study arms. A 2-sided p value ≤ 0.05 was considered significant for all tests. Continuous data are expressed as mean ± SD, whereas dichotomous data are summarized as frequencies for all other secondary comparisons. Due to incomplete patient enrollment, statistical analyses were restricted to the primary end point of in-stent late loss and to the predefined QCA, IVUS, and clinical secondary end points.

Results

The study was prematurely interrupted in April 2007, after 246 patients had been enrolled. This decision—made by the study principal investigators in consultation with the study sponsor, Conor Medsystems, and with concurrence of the data safety monitoring board—followed notification by the manufacturer of pimecrolimus, Novartis Corporation (Basel, Switzerland), of the preliminary results from an Avantec-sponsored (Sunnyvale, California) First-in-Man study evaluating the safety and efficacy of the Avantec pimecrolimus-eluting stent. Subsequently, the COSTAR II trial, also using the CoStar PES, failed to demonstrate noninferiority for the MACE primary end point when compared with the Taxus PES (Boston Scientific) (2). Commercial sale of the CoStar PES was then discontinued in the markets where it was already available. The investigators and the sponsor decided to analyze the data available on all enrolled patients at the time of trial suspension.

Study population, procedural and in-hospital outcomes. Among the 246 patients enrolled, 49 were randomized to CoStar, 97 to SymBio, and 100 to Corio (1 patient in the Corio Group received a Symbio stent) (Fig. 2). Baseline clinical characteristics of the patients as well as the angiographic and procedural characteristics of the lesions treated are shown in Table 1. No deaths occurred during the hospital stay. The rate of periprocedural MI was 5% in the Corio group versus 0% in the other 2 groups. Of the 5 periprocedural MIs, 4 were creatine kinase elevations alone without clinical sequelae, thought to be due to the procedure and not attributed to the stent. The fifth was an unsuccessful direct stenting, followed by predilation and successful stent placement complicated by a distal dissection that was unsuccessfully treated with 2 additional stents resulting in no flow.

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Table 1. Baseline Clinical and Procedural Characteristics of the Patients and the Lesions in the 2 Groups

	CoStar (n = 49)	SymBio (n = 97)	Corio (n = 100)	p Value
Age (yrs)	64.4 ± 9.8	59.9 ± 10.1	64.1 ± 10.0	
Male sex	35 (71.4%)	76 (78.4%)	80 (80%)	
Diabetes mellitus	18 (36.7%)	17 (17.5%)	32 (32%)	
Insulin dependent	3/18 (16.7%)	2/17 (11.8%)	15/32 (46.9%)	
Hypertension	36 (73.5%)	65 (67%)	66 (66%)	
Hypercholesterolemia	36 (73.5%)	69 (71.1%)	82 (82%)	
Current smoker	8 (16.3%)	38 (39%)	20 (20%)	
Prior myocardial infarction	11 (22.5%)	28 (28.9%)	26 (26%)	
Prior percutaneous intervention	13 (26.5%)	28 (28.9%)	33 (33%)	
Prior bypass surgery	3 (6.1%)	0	2 (2%)	
Unstable angina	10 (20.4%)	34 (35%)	25 (25%)	
Ejection fraction (%)	57.8 ± 8.9	63.7 ± 12.5	58.7 ± 12.1	
Glycoprotein IIb/IIa inhibitor	1 (2%)	5 (5.2%)	6 (6%)	
Target vessel				
Left anterior descending	20 (40.8%)	50 (51.5%)	49 (49%)	
Circumflex	12 (24.5%)	17 (17.8%)	24 (24%)	
Right coronary artery	17 (34.7%)	30 (30.7%)	27 (27%)	
ACC/AHA lesion type				
A	9 (18.4%)	22 (22.7%)	30 (30%)	
B1	14 (28.6%)	31 (31.9%)	31 (31%)	
B2	23 (46.9%)	29 (29.9%)	35 (35%)	
C	3 (6.1%)	15 (15.5%)	4 (4%)	
Direct stenting	29 (59.2%)	55 (56.7%)	53 (53%)	
After dilation	13 (26.5%)	34 (35%)	30 (30%)	
Max inflation pressure (atm)	14.2 ± 2.6	13.6 ± 2.6	13.9 ± 2.5	
Number of stents/lesion	1.04 ± 0.20	1.12 ± 0.41	1.12 ± 0.41	
1	47 (95.9%)	88 (90.7%)	91 (91%)	
2	2 (4.1%)	6 (6.2%)	6 (6%)	
3	0	3 (3.1%)	3 (3)	
Stent diameter used (mm)	(n = 50)	(n = 109)	(n = 112)	
2.5	10 (19.6%)	19 (17.4%)	25 (22.3%)	
3.0	24 (47.1%)	47 (43.1%)	62 (55.4%)	
3.5	17 (33.3%)	43 (39.5%)	25 (22.3%)	
Stent length used (mm)	(n = 51)	(n = 109)	(n = 112)	
10	9 (17.6%)	17 (15.6%)	15 (13.4%)	
16	24 (47.1%)	57 (52.3%)	64 (57.2%)	
22	12 (23.5%)	25 (22.9%)	24 (21.4%)	
28	6 (11.8%)	10 (9.2%)	9 (8.0%)	
Device success*	48 (98%)	95 (97.9%)	92 (92%)	0.11
Lesion success*	49 (100%)	97 (100%)	98 (98%)	0.68
Procedural success*	49 (100%)	97 (100%)	94 (94%)	0.02

Data are presented as n (%) or mean ± SD, unless otherwise specified. *Device success was not achieved when the post-procedural residual stenosis was >50% (n = 1), there was a device-related AE (n = 4), the device failed or malfunctioned (n = 2), or the treatment of the lesion was not completed with the assigned device only (n = 2) or any combination of the preceding (n = 2). Lesion Success was not achieved if the post-procedure residual stenosis was >50% (n = 2). Procedure Success was not achieved if lesion success was not achieved (n = 1) or the patient experienced a periprocedural major adverse cardiac event (n = 4) or both (n = 1).

ACC/AHA = American College of Cardiology/American Heart Association.

QCA and IVUS outcomes. In the Symbio group, 1 patient was lost to follow-up. At 6 months, 7 CoStar patients (14.3%), 2 SymBio patients (2.1%), and 7 Corio patients (7%) did not receive angiographic follow-up. Angiographic data are presented in Table 2. In-stent late loss was progressively and significantly higher with SymBio (0.96 ± 0.73 mm) and Corio (1.40 ± 0.67 mm) versus CoStar (0.58 ± 0.58 mm). On average, in-stent late loss of SymBio and of Corio was, respectively, 0.38 ± 0.13 mm and 0.82 ± 0.12 mm higher than CoStar ($p < 0.001$ for both). Thus, the

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Table 2. Quantitative Coronary Angiography Analysis of the Lesions Treated in the 3 Groups

	CoStar	SymBio	Corio	p Value
Before procedure	(n = 48)	(n = 97)	(n = 100)	
Reference vessel diameter (mm)	2.81 ± 0.47	2.87 ± 0.50	2.79 ± 0.46	
Minimal luminal diameter (mm)	0.72 ± 0.31	0.78 ± 0.37	0.76 ± 0.38	
Diameter stenosis (%)	74 ± 11	72 ± 13	73 ± 12	
Lesion length (mm)	14.4 ± 6	13.8 ± 5.4	14.9 ± 5.5	
After procedure	(n = 49)	(n = 97)	(n = 100)	
In-segment				
Minimal luminal diameter (mm)	2.41 ± 0.49	2.41 ± 0.45	2.33 ± 0.47	
Diameter stenosis (%)	16 ± 7	17 ± 6	18 ± 12	
Acute gain (mm)	1.69 ± 0.52	1.53 ± 0.46	1.57 ± 0.50	
Proximal edge				
Minimal luminal diameter (mm)	2.76 ± 0.53	2.83 ± 0.50	2.82 ± 0.52	
Diameter stenosis (%)	12 ± 8	12 ± 9	11 ± 8	
In-stent				
Minimal luminal diameter (mm)	2.82 ± 0.42	2.83 ± 0.39	2.81 ± 0.38	
Diameter stenosis (%)	5 ± 6	7 ± 6	6 ± 5	
Acute gain (mm)	2.10 ± 0.49	2.05 ± 0.46	2.04 ± 0.43	
Distal edge				
Minimal luminal diameter (mm)	2.53 ± 0.57	2.54 ± 0.53	2.47 ± 0.50	
Diameter stenosis (%)	10 ± ?	11 ± 9	12 ± 7	
Follow-up	(n = 42)	(n = 95)	(n = 95)	
In-segment				
Minimal luminal diameter (mm)	2.01 ± 0.61	1.71 ± 0.66	1.30 ± 0.69	<0.001
Diameter stenosis (%)	29 ± 16	40 ± 21	54 ± 22	
Proximal edge				
Minimal luminal diameter (mm)	2.59 ± 0.56	2.51 ± 0.71	2.59 ± 0.74	
Diameter stenosis (%)	11 ± 12	14 ± 18	15 ± 21	
In-stent				
Minimal luminal diameter (mm)	2.27 ± 0.64	1.89 ± 0.81	1.41 ± 0.75	<0.001
Diameter stenosis (%)	19 ± 19	33 ± 25	47 ± 25	
Distal edge				
Minimal luminal diameter (mm)	2.34 ± 0.60	2.29 ± 0.61	2.03 ± 0.75	
Diameter stenosis (%)	12 ± 10	13 ± 16	19 ± 21	
Late loss (mm)				
In-segment	0.42 ± 0.48	0.69 ± 0.58	1.07 ± 0.59	<0.001
In-stent	0.58 ± 0.56	0.96 ± 0.73	1.40 ± 0.67	<0.001
Binary angiographic restenosis				
In-stent	3 (7.1%)	19 (20%)	38 (40.9%)	<0.001
In-segment	4 (9.5%)	21 (22.1%)	42 (45.2%)	<0.001

Data are presented as mean ± SD or n (%).

primary end point of the study, noninferiority of SymBio or Corio in-stent late loss versus CoStar, was not met.

In-segment late loss and binary in-stent and -segment restenosis rates were also progressively higher with SymBio and Corio as compared with CoStar. Among the 4 CoStar in-segment restenoses, 3 were focal (75%) and 1 was diffuse (25%). Among the 21 SymBio restenoses, 10 were focal (48%), 7 were diffuse (33%), 3 were proliferative (14%), and 1 was occlusive (5%). Among the 42 Corio restenoses, 11 were focal (26%), 19 were diffuse (46%), 9 were proliferative (21%), and 3 were occlusive (7%).

The IVUS results, presented in Table 3 and representing a subset of enrolled patients, substantially confirm the QCA data of the complete cohort.

30-day and 6-month clinical outcomes. Clinical events are presented in Table 4. Between the end of the hospital stay and the first month after treatment, 1 additional MI, caused by early stent thrombosis and treated with percutaneous revascularization, was recorded in the Corio group. At 6 months, no cardiac deaths occurred, whereas 1 MI in the SymBio group (caused by late stent thrombosis, and treated with percutaneous revascularization) and 2 addi-

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Table 3. Intravascular Ultrasound Analysis of the Lesions Treated in the 3 IVUS Subgroups

	CoStar	SymBio	Corio	p Value
After procedure	(n = 29 analyzed = 14)	(n = 36 analyzed = 24)	(n = 32 analyzed = 17)	
Target segment length (mm)	20.1 ± 6.8	21.3 ± 8.7	20.4 ± 9.3	
Vessel volume (mm^3)	252.1 ± 109.4	281.6 ± 93.9	320.4 ± 139.1	
Stent volume (mm^3)	126.8 ± 42.9	145.5 ± 57.6	150.7 ± 77.8	
Lumen volume (mm^3)	125.6 ± 41.9	144.7 ± 57.6	149.9 ± 77.5	
Incomplete stent apposition	4/24 (16.7%)	8/27 (29.6%)	6/26 (23.1%)	
Follow-up	(n = 29 analyzed = 16)	(n = 36 analyzed = 26)	(n = 32 analyzed = 16)	
Target segment length (mm)	20.6 ± 5.4	21.0 ± 8.3	22.1 ± 9.3	
Vessel volume (mm^3)	319.3 ± 144.7	298.6 ± 160.6	330.3 ± 150.3	
Stent volume (mm^3)	148.6 ± 66.5	139.5 ± 55.6	161.4 ± 85.4	
Lumen volume (mm^3)	122.0 ± 50.5	100 ± 39.9	98.8 ± 62.3	
Neointimal volume (mm^3)	27.6 ± 28.6	39.5 ± 24.7	62.6 ± 29.4	
Percent volume obstruction (%)	16.6 ± 12	27.1 ± 12.4	41.2 ± 11.5	<0.001
Incomplete stent apposition	3/20 (15%)	5/28 (17.8%)	2/20 (10%)	0.91
Late acquired	0	0	0	
Persistent	3/20 (15.0%)	5/28 (17.8%)	2/20 (10.0%)	

Data are presented as mean ± SD or n (%).

tional MIs in the Corio group (both periprocedural during TVR) were recorded. According to the angiographic results, also the rates of TLR and TVR were progressively reduced by CoStar versus SymBio versus Corio, as was the cumulative MACE rate.

Discussion

Given the negative outcome of the CoStar II trial in which the CoStar paclitaxel-eluting stent was shown to be inferior to the Taxus-Liberte stent, one might question whether failure of the Conor reservoir technology is an explanation for the results in this trial. The data in this trial do not support this explanation, because the angiographic and clinical outcomes in the CoStar arm in this study are similar to those reported in the trials that led to CE Mark approval and are markedly better than historical data on bare metal stent outcomes in a similar cohort of patients. In fact, outcomes on the CoStar II trial were attributed to elution of paclitaxel, a drug with a narrow therapeutic index, at the lower end of the release kinetic specification in the CoStar stents used in this trial versus previous trials that, although within allowable specifications, were inadequate for the more complex 2-vessel disease patients studied in that trial. This conclusion was supported by a post hoc analysis demonstrating that noninferiority was met in patients with only single lesions in this trial (14). Additional evidence that the reservoir technology successfully delivered drug is the observation of clinical outcomes in the pimecrolimus arm that were worse than expected compared with historical bare metal stent data. Thus, there seem to be 3 main findings of this study comparing different drugs as eluted from the Conor reservoir-based stent: 1) pimecrolimus is not effective as an antirestenotic agent; 2) paclitaxel demonstrates activity as an antirestenotic agent; and 3) dual drug delivery with independent release kinetic and profile, using the Conor reservoir-based stent, is feasible.

Table 4. 30-Day and 6-Month Clinical Events in the 3 Groups

	CoStar (n = 49)	SymBio (n = 97)	Corio (n = 100)	p Value
30-day				
Death	0	0	0	
Myocardial infarction	0	0	6 (6%)	
Target vessel revascularization	0	0	1 (1%)	
Major adverse cardiac events	0	0	6 (6%)	0.02
Stent thrombosis	0	0	1 (1%)	
6-month				
Death	1 (2%)	0	0	
Cardiac death	0	0	0	
Myocardial infarction	0	1 (1%)	8 (8%)	
Target lesion revascularization	1 (2%)	14 (14.4%)	32 (32%)	<0.001
Target vessel revascularization	1 (2%)	14 (14.4%)	55 (55%)	
Major adverse cardiac events	1 (2%)	14 (14.4%)	39 (39%)	<0.001
Stent thrombosis	0	1 (1%)	1 (1%)	

Data are presented as n (%).

The unexpected outcome of this study was that the GENESIS trial failed to show a significant angiographic or clinical benefit of pimecrolimus. Although underpowered and not designed to assess clinical end points, the GENESIS trial outcomes suggest that in humans the drug might exacerbate the restenotic response, thus leading to results worse than those observed with bare metal stents. Indeed in the GENESIS trial, stents eluting only pimecrolimus

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showed the worst late loss, which compares unfavorably with the late loss reported in published reports for bare-metal stents in similar lesions and patients.

Pimecrolimus has been approved as topical treatment for inflammatory dermatologic diseases. Despite its "limus" name, it is not a rapamycin analogue. It is best classified as a tacrolimus analogue that exerts multiple anti-inflammatory effects, including inhibition of interleukin-2 synthesis via calcineurin inhibition and inhibition of interleukin-4, interferon-γ, and the release of inflammatory cytokines from mast cells. In contrast to other "limus" drugs, such as sirolimus, it does not bind to the mammalian target of rapamycin. Thus, it does not specifically exert antiproliferative actions, having no direct effect on cell cycle regulation. However, it has been assumed that it might do so indirectly by interleukin-2 inhibition. Several animal studies strongly suggested that it would be clinically effective in humans as an antirestenotic molecule when applied locally to atherosclerotic plaques treated with stent implantation (15,16).

However, the suggestions of clinical efficacy from the animal data were not confirmed by this current human study. The reasons for this failure are currently unknown. However, several explanations can be hypothesized. First, discrepancies in results between animal experiments and human trials are well known. The porcine model for the pathologic reaction to stent implantation is best-suited for determination of safety. Relative human efficacy is less predictable in this model and can only be definitely ascertained in clinical trials (17). Moreover, it is possible that, whereas inflammation can play an important role in neointimal proliferation in porcine stent models, the inflammatory response to stent implantation as affected by this drug might play a minor if not insignificant role as a determinant of the restenotic process in humans. Because pimecrolimus has no antiproliferative properties but mainly antiinflammatory and immunosuppressant actions, its lack of efficacy would tend to undermine the role of inflammation as central in the restenotic process in humans. Indeed, other drug-eluting stents aimed at inhibiting the inflammatory and immune reaction to stent implantation, such as stents eluting dexamethasone, failed to show benefits when compared with traditional bare-metal stents (18–20).

Despite market withdrawal, the CoStar PES provided encouraging results in this study, confirming the positive outcomes of previous trials, where this stent showed the lowest late loss among currently available PES (21,22) and superiority to the respective bare-metal stent (1). The outcomes of patients treated with CoStar in the GENESIS trial are similar to those reported in the COSTAR II trial, where examination of the outcomes suggested that the release of paclitaxel—a drug with a narrow therapeutic index—was insufficient for the more complex lesions and patients enrolled in the COSTAR II study (14).

The CoStar PES differs from other available drug-eluting stents, because it has the drug—mixed with a bioresorbable polymer—loaded in reservoirs cut into the stent rather than having the drug and the polymer on the surface of the stent. This property reduces the exposure of the vessel wall to the polymer and results in an inert bare-metal stent, after the elution of the drug and the dissolution of the polymer. Moreover, these technological advancements of the Conor stent platform—with its laser cut reservoirs and its bioresorbable polymer, which also allow controlled release of drugs—open the road to further investigations with different drugs loaded in the reservoirs and with specific release patterns, tailored to the different mechanisms involved in the pathophysiologic reaction to stent implantation. The GENESIS trial is the first trial to use the Conor reservoir technology to enable dual drug delivery for the treatment of coronary lesions. This trial has indeed demonstrated the ability to deliver 2 drugs independently, with each drug having a different effect on the tissue response to coronary intervention. The theoretical advantages of the delivery of more than 1 drug include the ability to release multiple agents that synergistically work on different mechanistic pathways to inhibit neointimal growth or produce other biologic effects. Other drugs of interest also include antithrombotic agents or pharmacological therapies that can inhibit reperfusion injury during acute MI.

Study limitations. The major limitation of this study was the early termination of enrollment. Thus, the study is underpowered for its primary angiographic end point. All analyses are post-hoc in nature: descriptive statistics only are presented for the primary and secondary end points, and no statistical analysis on differences in clinical end points (which the trial was not originally powered for) can be made. Moreover, the external validity of the trial is limited by the specific inclusion and exclusion criteria, thus limiting the applicability of the findings to the enrolled cohort of patients with selected lesions.

Conclusions

In native coronary artery lesions, stents eluting pimecrolimus or the dual combination of pimecrolimus and paclitaxel failed to show angiographic noninferiority when compared with paclitaxel-eluting stents.

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Key Words: coronary artery disease ▪ paclitaxel-eluting stent ▪ pimecrolimus-eluting stent ▪ restenosis.

The GENESIS (Randomized, Multicenter Study of the Pimecrolimus-Eluting and Pimecrolimus/Paclitaxel-Eluting Coronary Stent System in Patients with De Novo Lesions of the Native Coronary Arteries) Trial

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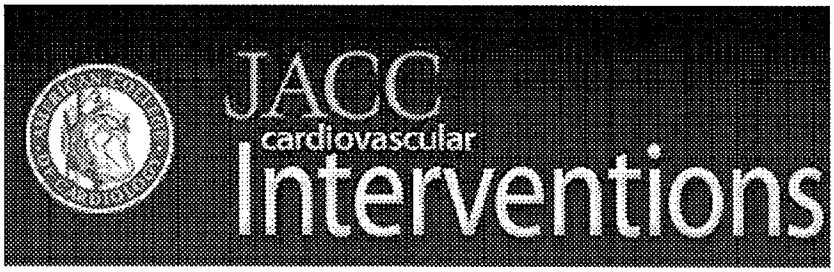

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Clinical and Angiographic Predictors of Recurrent Restenosis After Percutaneous Transluminal Rotational Atherectomy for Treatment of Diffuse In-Stent Restenosis

Juergen vom Dahl, MD, Peter W. Radke, MD, Phillip K. Haager, MD, Karl-Christian Koch, MD, Frank Kastrau, Thorsten Reffelmann, MD, Uwe Janssens, MD, Peter Hanrath, MD, and Heinrich G. Klues, MD

Due to the widespread use of stents in complex coronary lesions, stent restenosis represents an increasing problem, for which optimal treatment is under debate. "Debulking" of in-stent neointimal tissue using percutaneous transluminal rotational atherectomy (PTRA) offers an alternative approach to tissue compression and extrusion achieved by balloon angioplasty. One hundred patients (70 men, aged 58 ± 11 years) with a first in-stent restenosis underwent PTRA using an incremental burr size approach followed by adjunctive angioplasty. The average lesion length by quantitative angiography was 21 ± 8 mm (range 5 to 68) including 22 patients with a length ≥40 mm. Twenty-nine patients had complete stent occlusions with a lesion length of 44 ± 23 mm. Baseline diameter stenosis measured 78 ± 17%, was reduced to 32 ± 9% after PTRA, and further reduced to 21 ± 10% after adjunctive angioplasty. Primary PTRA was successful in 97 of 100 patients. Clinical success was 97%, whereas 2 patients developed non–Q-wave infarctions without clinical sequelae. Clinical follow-up was available for all patients at 5 ± 4 months without any cardiac event. Angiography in 72 patients revealed restenosis in 49%, with necessary target lesion reintervention in 35%. The incidence of rerestenosis correlated with the length of the primarily stented segment and the length of a first in-stent restenosis. Thus, PTRA offers an alternative approach to treat diffuse in-stent restenosis. Neointimal debulking of stenosed stents can be achieved effectively and safely. PTRA resulted in an acceptable recurrent restenosis rate in short and modestly diffuse lesion, whereas the restenosis rate in very long lesions remains high despite debulking. ©1999 by Excerpta Medica, Inc.

(Am J Cardiol 1999;83:862–867)

Optimal treatment of in-stent restenosis is yet to be defined. Currently, conventional balloon angioplasty is the preferred intervention, particularly in focal and short lesions.[1–3] Considering the mechanisms of in-stent restenosis with a large tissue mass resulting from smooth muscle cell proliferation and extracellular matrix accumulation, removal of in-stent neointimal tissue provides theoretical advantages over tissue compression and extrusion as well as additional stent overexpansion achieved by conventional percutaneous transluminal coronary angioplasty.[3] Therefore, debulking techniques such as directional atherectomy, laser angioplasty, or percutaneous transluminal rotational atherectomy (PTRA) have gained considerable interest, particularly in diffuse and long restenotic lesions. Preliminary data using PTRA for in-stent restenosis demonstrated the feasibility and safety of this technique.[4–7] This study addresses the acute success rate and predictors of the long-term effect of PTRA for treatment of restenosed stents, with special emphasis on long and diffuse restenotic lesions.

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METHODS

Patient selection: Patients with a first in-stent restenosis in native coronary arteries fulfilling the following criteria were prospectively and consecutively recruited: *inclusion criteria:* angina pectoris, and/or myocardial ischemia related to the target lesion, diameter stenosis ≥50% within or 5 mm proximal or distal to the stent edges, and stents implanted ≥3 months before this intervention; *exclusion criteria:* stents deployed at or directly distal to a bend of ≥45°, coil stents, recurrent in-stent restenosis, and missing visualization of the distal lumen after crossing the lesion with a guidewire or exchange catheter to verify correct wire position. The institutional ethical review board had approved the protocol and patients gave their written informed consent before participation.

Interventional procedure: The Coronary Rotablator or Rotalink Rotational Angioplasty Device (Boston Scientific Corp., Redmond, Washington) was used with an incremental burr size approach of steps ≤0.5 mm, achieving a burr/artery ratio ≥0.7.[8] Direct crossing of the lesion with the dedicated guidewire (Rotawire, Boston Scientific Corp.) was attempted. To avoid "dottering" of the lesion, exchange catheters were used only if primary crossing with the Rotawire was impossible or for visualization of the peripheral vessel in total occlusions. Slow burr passages (≤20 seconds) were performed at ≥165,000 rpm with sufficient pauses and saline flushing. Adjunctive percu-

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taneous transluminal coronary angioplasty was performed using the identical balloon size as for stent implantation or slightly oversized (≤0.5 mm) noncompliant or minimal compliant balloons.

Intravascular ultrasound was used in 88 of 100 patients. The decision to perform additional procedures such as coronary stenting within the target lesion to achieve an angiographically satisfactory result was at the discretion of the operator.

Clinical success was defined as procedural angiographic success (residual diameter stenosis <30% by visual assessment) in the absence of major adverse events during hospital stay.

Quantitative coronary angiography: Quantitative analysis was performed off-line from digitized cineangiograms using the Coronary Angiography Analysis System II (PieMedical, Maastricht, The Netherlands). Details of this edge-detection–based method and the use for assessment of stented lesions have been published previously.[9,10] Because of the lesion length and involvement of adjacent segments proximal and distal to the stent, a user-defined reference luminal diameter of a distal angiographically normal-appearing segment was chosen. The following parameters were measured: lesion length, reference luminal diameter, and minimal luminal diameter in millimeters; overall luminal diameter (mean of multiple measurements along the entire lesion length); and diameter stenosis in percentages at the location of the minimal luminal diameter.

Concomitant therapy: During the procedure, 10,000 IU of heparin was administered. Nitroglycerin (0.2 mg) was injected intracoronarily for optimal visualization of the stenosis before and after intervention to optimize quantitative analysis. No specific "cocktail" was given during PTRA. Patients received ticlopidine for 1 month and aspirin continuously.

Statistical analysis: Values are presented as mean ± 1 SD. The change in angiographic parameters from images immediately after the procedure to follow-up angiography was analyzed by pairwise comparison using the Wilcoxon rank-sum test. Unpaired data were analyzed by the Mann-Whitney U test. The influence of clinical and angiographic parameters on recurrent restenosis was analyzed using a stepwise logistic regression analysis. A p value <0.05 was considered to represent significant differences.

RESULTS

Patient characteristics and stent implantation: One hundred consecutive patients (70 men, aged 58 ± 11 years) were studied. Demographic, clinical, and angiographic characteristics are outlined in Table 1. In 57 patients, the initial stent implantation was the first percutaneous intervention, and 34 patients including 20 patients with stenting for restenosis had ≥1 previous nonsurgical coronary intervention.

The indication for stent implantation was a de novo lesion in 80% including chronic occlusions in 28% and a restenosed artery in 20%. The overall stent length was 31 ± 19 mm, with 2.1 ± 1.4 (range 1 to 6) stents per lesion and a 2.9 ± 0.3-mm (range 2.5 to 4.0) diameter. Stent implantation was performed with a mean implantation pressure of 16 ± 2 atm without systematic guidance by intravascular ultrasound. Implanted stents: Multi-Link, 36%; NIR, 23%; Wallstent, 19%; Palmaz-Schatz, 16%; PURA, 6%.

TABLE 1 Clinical, Procedural, and Angiographic Baseline Characteristics in 100 Patients Undergoing Rotational Atherectomy and Adjunctive Angioplasty for Diffuse In-Stent Restenosis

Age (yr)	58 ± 11
Men	70
Systemic hypertension (>160 mm Hg systolic and/or >90 mm Hg diastolic)	86
Hypercholesterolemia (>200 mg/dl)	78
Diabetes mellitus	42
Smoking history	58
Number of coronary arteries narrowed >50% in diameter	
1	40
2	32
>2	28
Left ventricular ejection fraction (%)	48 ± 12
Previous myocardial infarction	60
Previous bypass surgery	9
Target coronary artery	
Left anterior descending	40
Left circumflex	17
Right	43
Maximal burr size (mm)	1.9 ± 0.2
Burr/stent ratio	0.7 ± 0.3
Number of burrs used per intervention	2.1 ± 0.7
Burring time (sec)	125 ± 57
Balloon size, adjunctive angioplasty (mm)	3.2 ± 0.3
Inflation pressure, adjunctive angioplasty (atm)	9 ± 5
Total stent length (mm)	31 ± 19
Total lesion length (mm)	21 ± 8

Treatment of stent restenosis: PTRA was performed 177 ± 66 days after stent implantation. Details of the procedure are presented in Table I. Adjunctive balloon angioplasty was performed in 92 patients using 3.2 ± 0.3-mm balloons at 8 ± 5 atm. Residual stenosis after PTRA measured 32 ± 10% and was further reduced to 21 ± 10% after angioplasty (Table II). In 9 patients, additional 11 stents were implanted. Figures 1 and 2 illustrate the acute result in a complete recanalization of a previously recanalized and stented chronic occlusion of the right coronary artery.

PTRA was successful in 97%. In 2 patients, intracoronary ultrasound revealed incomplete expansion of stents, not visible by fluoroscopy, which were dilated with a short balloon followed by PTRA of the entire lesion. Another patient developed a long, asymptomatic, guidewire-induced dissection distal to an occluded stent without clinical sequelae, and the patient underwent a second successful attempt 2 weeks later.

There was no angiographically visible destruction of stents after PTRA. Intravascular ultrasound did not demonstrate any evidence of stent damage. During the procedure, 3 patients developed transient and asymptomatic "low flow," and reversible distal vessel spasm was observed in 6 patients.

Serial measurements of creatine kinase were 54 ± 27 IU at baseline, 68 ± 24 IU 6 hours after the procedure, and 62 ± 27 IU after 12 hours. Creatine

TABLE II Results of Quantitative Coronary Angiography

	Reference Luminal Diameter (mm)	Minimal Luminal Diameter (mm)	Overall Luminal Diameter (mm)	Stenosis (%)
Baseline	2.32 ± 0.42	0.56 ± 0.45	1.24 ± 0.84	76 ± 19
Poststent implantation	2.38 ± 0.38	2.29 ± 0.38	2.59 ± 0.33	12 ± 4
Before PTRA	2.25 ± 0.43	0.56 ± 0.44	1.25 ± 0.82	78 ± 17
After PTRA	2.35 ± 0.43	1.77 ± 0.19	2.10 ± 0.25	32 ± 10
After adjunctive angioplasty	2.31 ± 0.39	2.02 ± 0.23	2.36 ± 0.28	21 ± 10
6-month follow-up	2.28 ± 0.45	1.08 ± 0.65	1.71 ± 0.79	58 ± 25

Stenosis = diameter stenosis in percentages at the location of minimal luminal diameter.

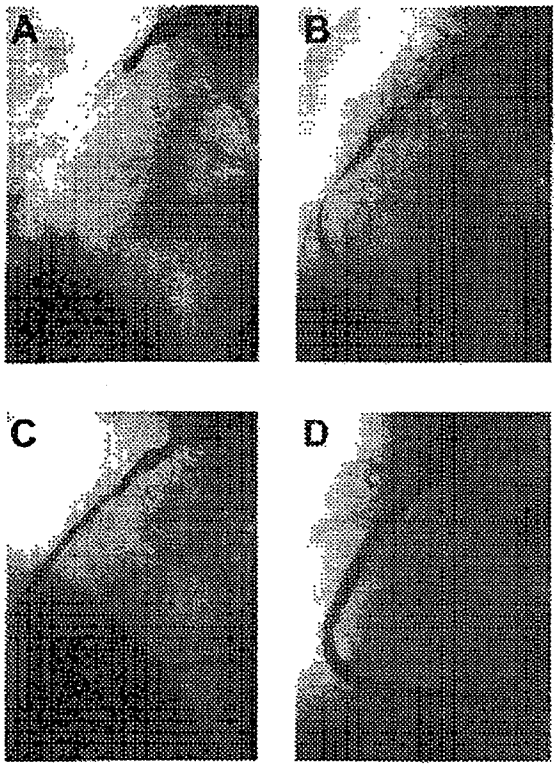

FIGURE 1. Acute results of PTRA in a 65-mm-long stent occlusion (one 25-mm Multi-Link and a 40-mm Wallstent) in the proximal and midpart of the right coronary artery. *A*, baseline situation; *B*, angiographic result after passage with a 1.5-mm burr. A clean channel is visible and the peripheral artery demonstrates anterograde flow; *C*, angiographic result after passage with a 2.51-mm burr; *D*, final result after adjunctive balloon dilatation with a 3.5-mm balloon at 4 atm.

kinase-MB values did not exceed 8% and postprocedural troponin T values were <0.2 ng/ml in 98 patients, whereas 2 patients had non–Q-wave myocardial infarctions without clinical sequelae during hospital stay. Overall, the procedure was clinically successful in 97 patients (including 2 with predilation for maldeployed stents).

Follow-up: Clinical follow-up over 5 ± 4 months (range 1 to 14) was available for all patients without any cardiac event or unscheduled hospitalization. Angina pectoris grade improved immediately after PTRA from class 3.1 ± 0.8 to 0.8 ± 0.6. At follow-up, 42% of patients were asymptomatic or in class 1, whereas 58% of patients were in Canadian Cardiovascular Society class 2 or 3 with a mean angina class in all patients of 1.9 ± 1.1.

Seventy-two patients underwent follow-up angiography after 128 ± 44 days. Nine asymptomatic patients refused angiography and 19 patients are not due for reangiography, with 16 of 19 being asymptomatic. Target lesion reintervention was necessary in 25 of 72 patients (35%). Bypass surgery was performed in 12 patients, and 13 patients were treated percutaneously. Overall, 35 of 72 patients (49%) had recurrent restenosis (>50% diameter) with 12 recurrent in-stent occlusions. Figure 3 illustrates the angiographic long-term outcome in a patient with diffuse in-stent stenosis in the left circumflex artery.

Factors influencing recurrent stent restenosis: The incidence of recurrent in-stent restenosis was significantly related to the length of the stented lesion and to the length of the first in-stent stenosis (Figure 4). Twenty-five patients with the need of target lesion reintervention had an initial restenosis length of 35 ± 14 mm and 23 of 25 had a restenosis length >20 mm before PTRA. In comparison, patients without need of reintervention had a lesion length of 22 ± 17 mm ($p < 0.05$). A stepwise logistic binary regression analysis including multiple clinical and angiographic variables revealed only the length of the stented lesion and the length of the first in-stent restenosis as independent predictors of recurrent restenosis (Table III).

All 12 patients with recurrent in-stent occlusion did have occluded stents before PTRA and all had chronic vessel occlusion before stent implantation, with a lesion length of 44 ± 14 mm. The initial length of the stented segments in these 12 patients was significantly longer than that in patients with nonocclusive high-grade in-stent stenosis (44 ± 14 vs 29 ± 12 mm, $p < 0.05$).

DISCUSSION

The results, although preliminary with regard to long-term follow-up, indicate that PTRA is a feasible and safe approach for treating symptomatic diffuse in-stent restenosis and achieves excellent acute results; there is clear tissue debulking within the restenosed lesion using PTRA; and the angiographic long-term outcome demonstrates good results in short or medium length (≤20 mm) lesions, whereas long and very diffuse lesions revealed a less favorable outcome.

Current treatment of in-stent restenosis: In-stent restenosis is caused by either inadequate stent expansion with low postprocedural diameter or, more often, by lumen encroachment from intimal hyperplasia, whereas mechanical recoil appears to be of minor importance.[30] The results of balloon angioplasty for in-stent restenosis demonstrate good acute angiographic outcome and clin-

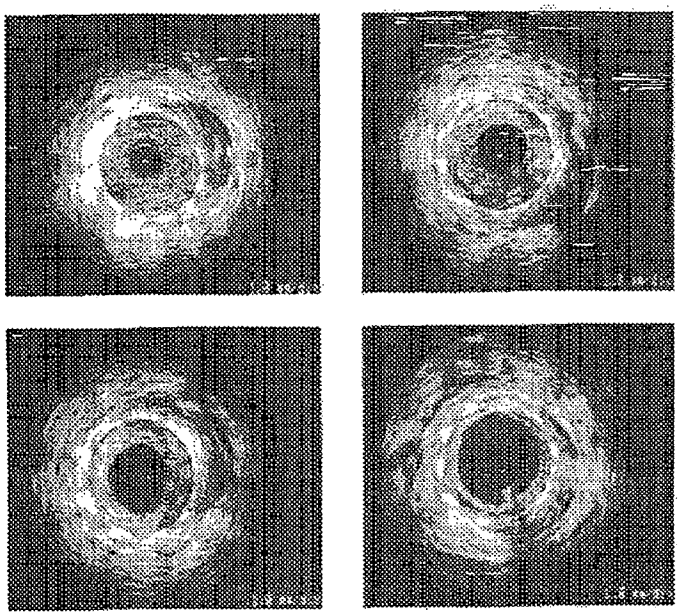

FIGURE 2. Intravascular ultrasound images of the patient illustrated in Figure 1. The baseline situation *(upper left)* displays complete neointimal filling of the lumen within the stent. The *upper right* image illustrates the new channel achieved by PTRA with the 1.5-mm burr. After PTRA with the 2.51-mm burr *(lower left)*, there is an additional increase in the lumen. Adjunctive balloon dilatation *(lower right)* leads to further tissue compression and extrusion without significant changes in stent diameter. A small neointimal tissue layer remains within the stent.

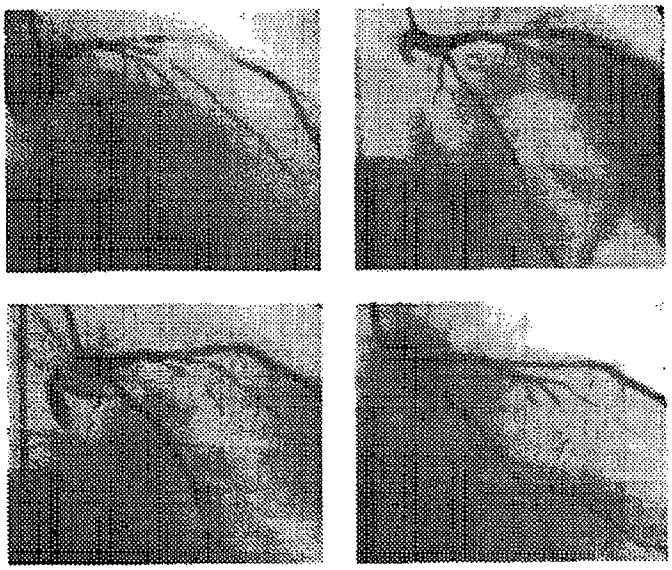

FIGURE 3. Acute and long-term results of PTRA and adjunctive percutaneous transluminal coronary angioplasty in 2 subtotally occluded 15-mm Multi-Link stents in the left circumflex artery. *Upper left*, baseline angiogram illustrating the 26-mm-long subtotal restenosis within two 3.0-mm Multi-Link stents with Thrombolysis In Myocardial Infarction (TIMI) trial I flow; *upper right*, after PTRA with a maximal burr size of 2.15 mm; *lower left*, result after adjunctive angioplasty with a 3.0-mm balloon at 9 atm; *lower right*, follow-up angiography at 6 months with TIMI 3 flow. Note focal restenosis in the midsection of the treated lesion demonstrating a 55% diameter reduction. Because the patient was asymptomatic with no evidence of exercise-induced ischemia during stress testing, no further intervention was attempted and the patient is still symptom-free at clinical 13-month follow-up.

ical long-term results in patients with short restenotic lesions.[12] However, the angiographic long-term results are associated with a wide range of restenosis, ranging from 30% to 57% with an average of 43%.[13] A recent study indicated an overall angiographic restenosis rate of 22%, with 14% in short lesions and 42% in diffuse (>10 mm) lesions.[6]

Other investigators have shown low restenosis rates for focal in-stent restenosis (12%), whereas long (>10 mm) and diffuse lesions restenosed in up to 85%.[14] These latter preliminary results appear comparable to the presented findings because most lesions treated with PTRA in our study demonstrated a long and diffuse pattern. Thus, a significant correlation between the length of the first in-stent restenosis and the probability of recurrent restenosis has to be expected regardless of which treatment approach is chosen.[15] Furthermore, similar to our results, all previous studies indicate an approximately 15% lower target lesion reintervention rate than the angiographically assessed restenosis rate.

Quantitative angiographic data during and immediately after balloon dilatation for in-stent restenosis are in good agreement with our quantitative data. Residual in-stent stenosis after angioplasty averaged 17% to 21%,[5,16] comparable to the 21% achieved after PTRA and adjunctive angioplasty. However, luminal enlargement by balloon dilation is limited to compression of tissue within the stent, and more importantly, to tissue extrusion through stent struts.[5,16] Furthermore, the use of oversized balloons or high pressure results in further stent expansion, but potentially induces vessel wall injury with deep adventitial stress forces. Nevertheless, as supported also by our results, treatment of in-stent restenosis does not recover the lumen dimensions of the initial stent implantation procedure.

Rotational atherectomy for in-stent restenosis: Previous clinical experiences demonstrated the ability of PTRA to remove plaque material, and have evaluated specific situations in which PTRA may be of greatest clinical usefulness.[17–19] PTRA causes atheroablation with only moderate evidence of barotrauma in coronary arteries, even after adjunct angioplasty, which may be advantageous in stents.[20] Our observations demonstrate the safety and technical success of PTRA using a conservative stepped burr approach and attention to preventing decreases of >5,000 rpm. Besides the 2 uneventful cases of stent un-

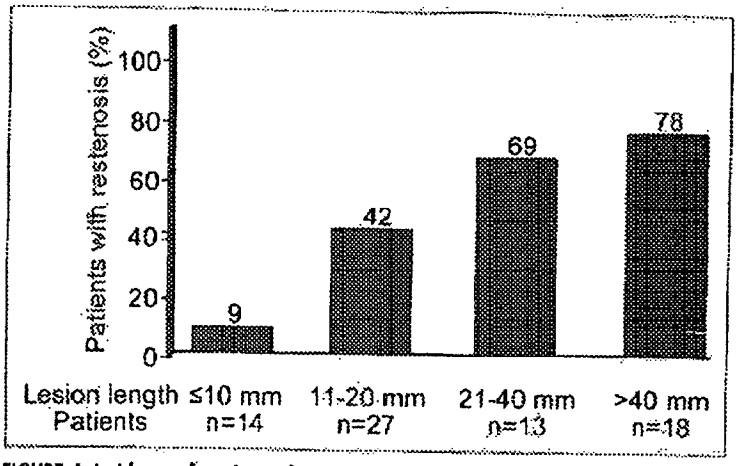

FIGURE 4. Incidence of angiographic recurrent restenosis, defined as >50% diameter stenosis at follow-up, correlating with the length of the initially treated stent restenosis.

TABLE III Clinical, Procedural, and Angiographic Risk Factors of Recurrent Angiographic Restenosis at Six-Month Follow-Up in 72 Patients After Rotational Atherectomy for Diffuse In-Stent Restenosis

	Restenosis (n = 35)	No Restenosis (n = 37)
Age (yr)	57 ± 12	58 ± 9
Men	23 (66%)	26 (70%)
Diabetes mellitus	17 (49%)	11 (30%)
Number of coronary arteries narrowed >50% in diameter		
1	13 (37%)	16 (46%)
2	10 (29%)	12 (32%)
>2	12 (34%)	9 (24%)
Left ventricular ejection fraction (%)	46 ± 14	49 ± 8
Previous bypass surgery	4 (11%)	4 (11%)
Target coronary artery		
Left anterior descending	12 (34%)	16 (43%)
Left circumflex	5 (14%)	7 (19%)
Right	18 (51%)	14 (38%)
Maximal burr size (mm)	2.1 ± 0.3	2.1 ± 0.4
Burr/stent ratio	0.68 ± 0.25	0.72 ± 0.30
Number of burrs per intervention	2.0 ± 0.6	2.1 ± 0.4
Burring time per intervention (sec)	119 ± 67	129 ± 55
Balloon size, adjunctive angioplasty (mm)	3.1 ± 0.4	3.2 ± 0.3
Inflation pressure, adjunctive angioplasty (atm)	8 ± 6	7 ± 6
Total stent length (mm)	41 ± 21*	19 ± 12*
Total lesion length (mm)	34 ± 19†	13 ± 9†

*p = 0.008, †p = 0.009.

derexpansion, there were no adverse effects associated with the use of the device and no in-hospital complications occurred. These 2 cases illustrate the particular usefulness of preinterventional intracoronary ultrasound in situations in which no exact information about the stent implantation procedure are available to choose the appropriate burr size, because fluoroscopic visibility of implanted stents is often poor.[15]

Previous studies support the safety of PTRA for in-stent restenosis.[4,7,9,11,22] Comparisons between PTCA alone or in combination with debulking approaches have been reported recently and indicated favorable results for patients treated with a debulking device.[23,24] However, angiographic follow-up data have not been reported yet in a larger patient cohort.

Compared with PTRA in native and calcified vessels, the technique is associated in restenosed stents with a low incidence of "slow flow" or vessel spasm. Similarly, the 2% rate of non–Q-wave infarctions was low compared with previous studies indicating 5% to 10% enzyme elevations after PTRA of native and calcified vessels.[9] Stent destruction or migration could not be demonstrated either by angiography or by intravascular ultrasound. However, the true local effect of the spinning device with direct contact to the stent struts remains unclear. Some abrasion of metal due to eccentric burr positioning, particularly in curves cannot be ruled out but obviously does not result in clinical sequelae.

PTRA is most often used in combination with adjunctive angioplasty. Whether PTRA as a "stand alone" procedure will reduce repeat vessel trauma compared with combined intervention, certainly at the cost of a smaller postprocedural minimal lumen diameter, has to be further evaluated. "Low pressure" inflations could represent a compromise between the concepts of optimal acute angiographic results achieved by adjunctive high-pressure inflation versus the "purist" approach of debulking without adjunctive balloon dilation. Furthermore, early tissue reinfusion into the stent needs further evaluation by intravascular ultrasound.

With regard to the long-term results, our data with a 35% target lesion reintervention rate in the setting of this "negative selection" are similar to preliminary data from other centers. Sharma et al[25] recently reported a target lesion reintervention rate of 28% after PTRA. They proposed diffuse (>10 mm) in-stent restenosis, ostial lesions, and a burr/artery ratio <0.6 as predictors of recurrent restenosis. However, in our study with relatively small vessels the burr/artery ratio was not predictive for repeat restenosis. Buettner et al[26] reported angiographic restenosis in 56%, with 33% reinterventions in 27 patients with a mean lesion length of 18 mm.

It appears very likely from the results of this study and from previously cited studies that very long and diffuse restenotic lesions have an unfavorable long-term outcome with regard to recurrent lumen narrowing despite angiographically successful tissue removal

after PTRA. New approaches such as intracoronary brachytherapy[27,28] or pharmacologic blockade of the platelet glycoprotein IIb/IIIa receptor[29] either to reduce restenosis and the need for reintervention or to improve the outcome of treating in-stent restenosis[30] will be evaluated in the near future to overcome this challenging problem in interventional cardiology.

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Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis

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Late Total Occlusion After Intracoronary Brachytherapy for Patients With In-Stent Restenosis

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OBJECTIVES The study sought to determine the incidence and predictors of late total occlusion (LTO, >30 days) in-patients with in-stent restenosis who were treated with intracoronary radiation.

BACKGROUND Intracoronary radiation both with beta and gamma emitters has been shown to reduce recurrent in-stent restenosis.

METHODS We reviewed the records of 473 patients who presented with in-stent restenosis and who were enrolled in various radiation protocols, whether randomized to placebo versus radiation or entered into registries. There were 165 placebo and 308 radiated patients, including both gamma and beta emitters. Maximum dose to the vessel wall was 30 to 55 Gy. Following radiation, all patients received antiplatelet therapy with aspirin and either ticlopidine or clopidogrel for one month. All patients completed at least six months of angiographic follow-up.

RESULTS The LTO was documented in 28 patients (9.1%) from the irradiated group versus 2 placebo patients (1.2%), $p < 0.0001$. The LTO rates were similar across studies and emitters. In the irradiated group, LTO presented as acute myocardial infarction in 12 patients (43%), unstable angina in 14 (50%), and asymptotic in 2 (7%). Mean time to LTO was 5.4 ± 3.2 months in the irradiated group versus 4.5 ± 2.1 in placebo patients (p = NS). The overall rate of restenting for the entire study group at the time of radiation was 48.6%. Importantly, new stents were placed in 82% of the irradiated and in 100% of the placebo patients *who presented with LTO*. Multivariate analysis determined that new stenting was the main predictor of LTO.

CONCLUSIONS Intracoronary radiation for patients with in-stent restenosis is associated with a high rate of LTO. Restenting may contribute late thrombosis. Prolonged antiplatelet therapy (up to six months) should be considered for these patients. (J Am Coll Cardiol 2000;36:65–8) © 2000 by the American College of Cardiology

Vascular brachytherapy is effective in preventing restenosis. Preclinical studies utilizing both beta and gamma emitters have shown a reduction of smooth muscle proliferation, prevention of late contraction, and a delayed healing response following vascular injury (1–4).

An important clinical application of vascular brachytherapy is as adjunct therapy for the treatment of in-stent restenosis. Several studies, including three randomized trials, have shown a reduction in recurrent in-stent restenosis of 50% to 70% compared to conventional therapy (5–9). However, radiation has been reported to induce thrombosis. Previous studies on the vascular effects of external beam radiation have suggested that increased thrombosis is a complication of delayed healing (10,11).

Thrombotic occlusion following balloon angioplasty usually occurs either immediately or within 24 hours following intervention. Stents are more often associated with subacute thrombosis (within 30 days of implantation), which is well controlled using antiplatelet therapy for 15 days (12–15). Among the complications associated with vascular brachytherapy is a new phenomenon of late coronary thrombosis (>30 days) (16,17).

The purpose of the current study was to determine the rate of late total occlusion (LTO) following brachytherapy for in-stent restenosis as well as its clinical presentation and predictors.

METHODS

From February 1997 to December 1998, a total of 473 patients with in-stent restenosis at the Washington Hospital Center were enrolled into six randomized vascular brachytherapy trials—WRIST (Washington Radiation for In-Stent restenosis Trial), LONG WRIST (long in-stent restenosis lesions 36 to 80 mm), SVG WRIST (in-stent restenosis in vein grafts), GAMMA-1, ARTISTIC (Angiorad Radiation Therapy for In-Stent restenosis Trial in Coronaries), PREVENT (Proliferation Reduction with Vascular Energy Trial)—and into two registries, BETA WRIST (beta radiation for in-stent restenosis) and LONG WRIST HIGH DOSE (long lesions 36 to 80 mm using 15 Gy at 2.4 mm at the perspiration point). All clinical trials were approved by the Food and Drug Administration and

From the Cardiac Catheterization Laboratories, Washington Hospital Center, Washington, D.C. This research was supported by the Cardiovascular Research Foundation, Washington, D.C. Dr. Ron Waksman is entitled to receive royalties from Emory University on his inventions in the field, and he serves as a consultant to several companies doing work in vascular brachytherapy.

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